III. REMARKS

A. Status of the Claims:

Claims 1-30 and 87-93 have been examined and rejected under 35 U.S.C. § 112 ¶ 2 and § 102 (b). The rejection is addressed in detail below. Claims 1-8, 17-24, 26-30, 87-90, and 93 have been amended to claim the subject matter with more particularity. No new matter is introduced in the amendments, entry thereof is respectfully requested.

B. Informalities:

The specification has been amended to correct certain informalities stated below:

a. The disclosure at page 38, line 16 is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicants have deleted the hyperlink pursuant to the Examiner's suggestion. Withdrawal of this objection is respectfully requested.

b. The disclosure at page 71, paragraph 202 is objected to for failing to include a SEQ ID NO to the polypeptide shown in line 2. Applicants have amended the disclosure to specify that the polypeptide corresponds to residues 1 through 6 of SEQ ID NOS. 2 or 4. Applicants submit that such amendment overcomes the objection and satisfies the sequence listing requirements of 37 C.F.R. §§1.821-1.825.

C. Claim Rejections

1. Rejection under 35 U.S.C. § 112

Claims 1-30, 87-93 are rejected under 35 U.S.C. 112, ¶ 2, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 3, 22, and their dependents are rejected for reciting allegedly an indefinite phrase, i.e., "sequences that mediate heterodimerization of the receptors." The Examiner opines that it is unclear whether the term "receptors" is used to modify the heterodimeric receptor sequences. The claims are amended to specify that the first and second herterodimerization polypeptides comprise "*polypeptides from heterodimeric receptors that mediate heterodimerization of said receptors*," thus obviating the ambiguity, if any, present in the original claims.

b. Claims 1-30, 87-93 are rejected for reciting the term "sequences." The Examiner indicates that "sequence" refers to information describing the amino acid sequence, and not chemical structure. Applicants respectfully submit that the term "sequence" as used in the instant application clearly embodies the structural elements - "polypeptides." For instance, the description at page 29, paragraph 92 states:

> In the context of polypeptides, a "linear sequence" or a "sequence" is an order of amino acids in a polypeptide in an amino to carboxyl terminus direction in which residues that neighbor each other in the sequence are contiguous in the primary structure of the polypeptide.

However, for ease of prosecution, Applicants have replaced the term "sequence" with "polypeptide." Such amendment does not alter the scope of the originally present claim element, and as such, are entitled to the same doctrine of equivalents treatment that would have been available for the original claims.

c. Claims 8, 18, 19, 29-30 and their dependents are rejected for reciting the phrase "first and second heterodimerization sequences are linked to at least one cysteine residue." The Examiner points out that it is not clear if the first and second heterodimerization amino acid

sequences are linked to each other by a disulfide bond or if the heterodimerization amino acids sequences are connected to the VL or VH by a cysteine residue.

The claims as amended now specify that the "*first and second heterodimerization polypeptides are linked to each other by a disulfide bond*", thus obviating the ambiguity. Applicants respectfully request withdrawal of this rejection.

d. Claims 18, 19, 29-30 and their dependents are rejected for reciting the terms "essentially identical" and "comparable length."

Applicants respectfully submit that these terms are defined in the specification as originally filed. For instance, the specification at page 40, paragraph 120 sets forth the percentage of homology that is required to establish "essential identity." Paragraph 120 states the following:

> A linear sequence of peptide is "essentially identical" to another linear sequence, if both sequences exhibit substantial amino acid sequence homology. Generally, essentially identical sequences are at least about 60% identical with each other, after alignment of the homologous regions. Preferably, the sequences are at least about 70% identical; more preferably, they are at least about 80% identical; more preferably, they are at least about 90% identical; more preferably, the sequences are at least about 95% identical; still more preferably, the sequences are 100% identical.

The description further provides that essential identity must be compared after alignment of the homologous region. The claim language, taken as a whole, instructs which of the sequences being compared is used to calculate the identity. As such, the previously presented claims 18-19, 29-30 and their dependents comply with the requirements of 35 USC § 112 ¶ 2.

However, in a sincere effort to place this application in condition of allowance, Applicants have amended the claims to require that the linear sequence to be compared is

identical in length to the claimed $GABA_B$ receptor polypeptide. Withdrawal of this rejection is respectfully requested.

e. Claims 17, 26-28 are allegedly indefinite for reciting "derived." Applicants respectfully point out that the term "derived" is adequately defined in the specification. The specification not only defines "derived from" as designating the origin of the polypeptide, but also provides structural limitations of preferred derivatives (see, e.g., page 18 paragraph 65, page 40 paragraph 122). The specification further sets forth various functional criteria for derivatives as instantly claimed (see, e.g., page 40, paragraph 121).

Although Applicants do not agree with the grounds of rejection, the language objected to has been deleted. Applicants assert that the claims as amended are entitled to the same doctrine of equivalents treatment that would have been available for the originally presented claims. Withdrawal of this rejection is respectfully requested.

f. Claims 20 and 22 and their dependents are allegedly indefinite. Specifically, the Examiner points out that the phrase "a first and a second heterodimerization sequences spanning the distance between the C-terminus of one of the region to the N-terminus of the other region" can be interpreted to embody more than one antigen-binding unit configuration.

The claims as originally presented recite a defined type of single-chain antigen-binding unit. The claims require that the VL and VH regions contained in such antigen-binding unit to "*form an intra-molecular dimer via pairwise affinity of the first and second heterodimerization polypeptides*". The claim language excludes a particular configuration raised by the Examiner, in which a single-chain antigen-binding unit is connected to dimerization domain (VH-VL-domain-domain-VH-VL). In this cited configuration, the dimerization domain is used to connect

two existing antigen-binding sites, and not to dimerize VH and VL to form one antigen-binding site.

To further clarify the alleged ambiguities, claims 20 and 22 are amended to reference the antigen-binding units "*as shown in Figure 18*". Consistent with the original claim language, Figure 18 depicts two single-chain antigen-binding units, each of which has a single antigen-binding site formed by dimerization of the VL (light chain variable region) and VH (heavy chain variable region). The VL and VH regions form an intra-molecular dimer via pairwise affinity of the first and second heterodimerization polypeptides. As such, the claims clearly define a single-chain antigen-binding unit distinct from the cited configuration, thereby obviating the ambiguities, if any, present in the original claims. Withdrawal of this rejection is respectfully requested.

2. Rejection Under 35 U.S.C. § 102

Claims 20-21, 23-27 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Pluckthun et al. (Immunotechnology 3:83-105, 1997). This rejection is based on the interpretation that claims 20-21, and 23-27 cover the single-chain antigen-binding unit connected to a dimerization domain (VH-VL-domain domain-VH-VL). As noted above and elaborated further below, the claim language precludes VH-VL-domain domain-VH-VL configuration.

Pluckthun et al. teach multivalent (e.g., dimeric and tetrameric) antibodies that have more than one antigen-binding site formed by VH and VL (see Figure 3). The multiple antigen-binding sites are then connected together via a dimerization domain. By contrast, the claimed antigen-binding unit is a monovalent single chain, i.e., containing a single antigen-binding site. The VH and VL regions of this single-chain molecule form an intra-molecular dimer via pairwise affinity of a first and second heterodimerization polypeptides. Thus, the claimed

antigen-binding units are distinct from the cited molecules. As such, Pluckthun et al. does not read on the rejected claims.

Moreover, Pluckthun et al. does not teach or even suggest the particular type of heterodimerization sequences as instantly claimed. The subject heterodimerization sequences exhibit unique functional and/or structural characteristics, which are not taught or even suggested by Pluckthun. For instance, the subject heterodimerization sequences require that at least one of the heterodimerization polypeptides is essentially incapable of forming a homodimer under physiological buffer conditions and/or at physiological body temperatures. Alternatively, the subject heterodimerization sequences comprise polypeptides from heterodimeric receptors that mediate heterodimerization of the receptors.

The Examiner cites the descriptions in Pluckthun at pages 99 and 101, which show that Pluckthun recognized the shortcomings of previously described heterodimerization sequences, but failed to provide a solution or even a suggestion as to how to come up with an improved heterodimerizsation sequence. At page 99, Pluckthun states:

> "The co-expression of fos- and jun-baed miniantibodies (Table 1) in one cell leads mainly to separate jun-jun and fos-fos homodimers and partial degradation of the fos sequences.... The improvement of such hererodimerizsation domain requires the careful modifications of the coiled coil sequences."

As is apparent to one skilled in the art, such description merely states the problem but fails to suggest what modifications, functional or structural, that is required to solve the problem. The mere assertion that careful modification is required does not enable one skilled in the art to derive the claimed invention. As such, Applicants submit that the cited art neither anticipates nor renders the claimed antigen-binding units obvious. Withdrawal of this rejection is respectfully requested.

III. CONCLUSION

Applicants respectfully submit that the above amendments and remarks fully respond to the rejection made in the Office Action mailed April 11, 2003. Applicants submit that the claims as amended are in allowable form and condition. The Examiner is invited to call the undersigned at (650) 463-8172 with any questions, comments or suggestions relating to this application.

Should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Commissioner is authorized to deduct said fees from the deposit account of Howrey Simon Arnold & White, LLP, Deposit Account No. **08-3038**, referencing Docket No. **13403.004.NPUS00**.

Respectfully submitted,

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